REMARKS/ARGUMENTS

I. Status of the Claims

Claims 71-114 are under consideration in the instant application. These claims stand variously rejected under 35 U.S.C. §112 first paragraph for lack of enablement and lack of written description, under obviousness-type double-patenting and 35 U.S.C. §112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the invention. Applicants respectfully traverse the rejection.

II. Rejection under 35 U.S.C. §101

Claim 71 was rejected under 35 U.S.C. §101 as assertedly being directed to non-statutory subject matter. The rejection states that the claim reads on a product of nature in that the claimed polypeptide is not isolated. Initially, Applicants disagree with the rejection because claim 71 does not claim just to the nascent polypeptide as it is found in nature, but instead a composition that comprises an SCF polypeptide and at least one cytokine, ***in a pharmaceutically acceptable carrier.*** Applicants have nevertheless amended the claim to read "isolated SCF" as suggested by the Examiner. Applicants believe this amendment addresses the grounds for rejection and request that the rejection be withdrawn.

III. Obviousness-type Double-Patenting Rejections

In a prior Office Action (July 20, 2001), the Examiner provisionally rejected the claims of the present under obviousness-type double patenting over U.S. Patent No. 6,204,363. Applicants thank the Examiner for holding the rejection in abeyance until the filing of the terminal disclaimer. Applicants provide a terminal disclaimer with respect to the double-patenting rejection over U.S. Patent 6,204,363.

In the Office Action dated November 29, 2002, the Examiner further rejected the claim under obviousness-type double patenting over the co-pending U.S. Patent Application No. 09/643,652. Applicants traverse the rejection with respect to co-pending U.S. Patent Application No. 09/643,652. Applicants submit that the claims of that application were initially cancelled and substitute "methods" claims were presented in a preliminary amendment filed with the

application papers on August 21, 2000. However, the preliminary amendment was not entered by the United States Patent and Trademark Office. It is Applicants contention that the claims of that application should have been directed to the methods claims presented in said preliminary amendment. Applicants are in the process of clarifying this with the Examiner. In any event, Applicants request that this latter double-patenting rejection be held in abeyance until Applicants have had an opportunity to resolve this matter.

IV. Rejection of the Claims Under 35 U.S.C. §112, First Paragraph for Lack of Enablement Should be Withdrawn.

The Examiner maintained the rejection of claim 71-114 under 35 U.S.C. §112, first paragraph as assertedly not being enabled by the specification. Applicants respectfully traverse and provide the following discussion for the Examiner's consideration.

a. The specification provides express working examples of how to make and use the claimed invention.

Initially Applicants wish to point out that in order to expedite prosecution of claim 71, it has been amended to remove recitations to analogs such that the claim recites:

> A composition which comprises a therapeutically effective amount of an isolated stem cell factor (SCF) polypeptide, or a biologically active SCF fragment comprising at least 130 contiguous amino acids of any of sequences set forth in SEQ ID NO:46, SEQ ID NO:61 or SEQ ID NO:63 that possesses an activity associated with SCF and one or more cytokines in a pharmaceutically acceptable carrier.

The analogs of SCF are presented in new claim 115, and are separately discussed at length in section IV(d) below. Thus, the composition of the independent claim 71 is directed to an isolated SCF polypeptide, or a biologically active fragment of a stem cell factor that possesses an activity associated with stem cell factor. Applicants submit that both factually and as a matter of law, the specification provides the requisite enablement for the claimed subject matter.

The specification as filed teaches that SCF has a "central role in embryogenesis and hematopoiesis" and demonstrates its "capacity for treatment of various stem cell deficiencies."

(specification page 18, lines 20-24). The full length human stem cell factor is 248 amino acids in length. The specification further teaches a number of assays to monitor stem cell factor activity. For example, as indicated in the previous response, one of skill in the art could use the disclosure at pages 31-34, to determine the effect of a given SCF, or SCF fragment, on early hematopoietic cells (high proliferation potential colony forming cell (HPP-CFC) assay); it teaches how to determine whether a given SCF will cause proliferation of an IL-4 dependent murine cell line (using a MC/9 assay); and how to evaluate the effect of a given SCF on normal undepleted bone marrow (using a CFU-GM assay). The specification also taught how to determine the effects of a SCF composition *in vivo.*, see *e.g.*, the teaching that SCF corrects macrocytic anemia and other phenotypic disorders of a bone marrow transplant mouse model and the tests performed in primates (page 108). Additionally, Applicants point out that these latter primate tests were performed using the ***fragments*** ($hSCF^{164}$ and $hSCF^{165}$). With the above discussion in mind, Applicants address each of the Examiner's reasons for maintaining the rejection individually.

b. The rejection for lack of enablement is incorrect as a matter of law as set forth by the Federal Circuit and as discussed in the MPEP.

At page 6 of the Office Action, paper 16, the Examiner, having summarized some of Applicants previously filed discussion, stated that "since the specification does not teach all possible 'biologically active' fragments and analogs of the SCF polypeptide, undue experimentation would be required to determine how to use a 'biologically active' fragment or analog." The Examiner further laments that the application does not "teach any methods or working examples that indicate which specific activity is associated with a 'biologically active' fragment."

Applicants object to the above rejection as applying the wrong standard for enablement. The enablement requirements of the statute are satisfied when the specification disclosure, ***taken with the teachings in the art***, teaches an effective process for making and using the claimed compositions from known starting materials, and the specification describes methods of using the claimed compositions. *Ex parte Gastambide, Thal, Rohrbacj and Laroche*, 189 USPQ 643, 645 (PTO Bd. App. 1974). Thus, all that is required is that the Applicant objectively enable the claimed invention. The law has never required that the Applicant provide specific working examples. The Examiner guided Applicants to review MPEP §2164.06, which

the Examiner cited as indicating that ". . . guidance and ease in carrying out an assay to achieve the claimed objectives may be an issue to be considered in determining the quantity of experimentation needed. For example, if a very difficult and time consuming assay is needed to identify a compound within the scope of a claim, then this great quantity of experimentation should be considered in the overall analysis." However, the very next sentence of that section of the MPEP states that "[t]ime and difficulty of experiments are not determinative if they are merely routine." As Applicants have previously discussed, the experimentation required for the instant application is nothing more than mere routine. The factors that are discussed in the section of the MPEP cited by the Examiner are the factors from *In re Wands*, which all point to Applicants' claimed invention being found to be enabled, as discussed in the Response to the Office Action filed September 20, 2002 (incorporated herein by reference).

Reviewing MPEP § 2164.01 further, Applicants find additional support for the fact that the instant application provides an enabling disclosure commensurate in scope of the claims of the application. MPEP § 2164.01(b) provides specific examples in the case law of decisions ruling that the disclosure was either non-enabling or enabling. Under the former category, the MPEP cites a number of decisions including *In re Wright*, 999 F.2d 1557, 27 USPQ2d 1510 (Fed. Cir. 1993); and *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993). The latter category cited, amongst other decisions, *In re Wands*, and *In re Bundy*, 642 F.2d 430, 434, 209 USPQ 48, 51-52 (CCPA 1981). The facts and analysis of the present case are more akin to *In re Wands* and *In re Bundy* than to *In re Wright* and *In re Goodman*.

In both *In re Wright* and in *In re Goodman* there was specific evidence that cast doubt on the scope of the claimed invention. For example, in *In re Wright*, the Examiner provided a teaching from the art that compositions of the claimed scope ". . . remained an intractable problem" and that "this evidence, along with evidence that RNA viruses were a diverse and complicated genus" led the Federal Circuit to conclude that the invention was not enabled. ***That is not the case here.*** Stem cell factor is not a "diverse and complicated genus". Full-length SCF is a protein having 248 amino acids. The teachings of the specification specifically exemplify numerous SCF fragment sequences that have activities associated with the full length SCF sequences and methods of determining the SCF activity of other fragments that one of skill in the art could readily generate. The Examiner has provided no evidence that the use of stem cell

factor in a pharmaceutical composition along with one or more cytokines presents an intractable problem.

The facts of the present case are more akin to *In re Wands*. In that case the court indicated that the sole issue in that case was "whether it would require undue experimentation to produce high-affinity IgM monoclonal antibodies." The court specifically noted that no undue experimentation is required to practice an invention if the material being claimed can be made from readily available starting material through routine screening *Id.* at 739. As a corollary, in the present case a starting material for making fragments of an SCF may be any of the SCF proteins exemplified in the specification, for example, such a protein may be the 248 amino acid sequence SCF exemplified in the specification. Once that sequence is known, those of skill can readily make fragments because, much like the technology for making hybridomas that was in question in *In re Wands*, the techniques for generating fragments of a protein sequence are well known to those of skill in the art. The mere fact that a large number of fragments could be generated does not preclude enablement. As the Federal Circuit indicated, a determination of undue experimentation "cannot be made solely be reference to a particular numerical cutoff." Hence, Applicants submit the Examiner's interpretation of the enablement requirements of 35 U.S.C. §112, first paragraph are incorrect in light of the case law.

c. The examiner has mischaracterized the teachings of the specification.

At page 6 of the Office Action, the Examiner cites to the specification page 185, lines 23-26 and states that this section of the specification "guides the skilled artisan that at least 1-130 amino acids of SCF are required for the activity of enhancement of hematopoiesis. The specification does not disclose that SCF fragments shorter than 130 amino acids have any specific activity." Applicants respectfully submit that this is an overly inflexible and restrictive interpretation of the teachings of the specification. The same mischaracterization is again repeated at page 10, and page 11 of the Office Action.

Firstly, the section of the specification referred to by the Examiner states:

> SCF^{1-130} has lowered specific activity in both the radioreceptor assay (about ***50% of the value for*** SCF^{1-164}) and the UT-7 assay

> (about ***15% of the value for SCF$^{1-164}$***). SCF$^{1-137}$ has full specific activity in the radioreceptor assay but lowered specific activity in the UT-7 assay (about 25% of the value for SCF$^{1-164}$ and SCF$^{1-165}$); this analog therefore may be preferable as an SCF antagonist in situations where it would be advantageous to block the biological activity of SCF.

While this section of the specification may well teach that some fragments have a reduced specific activity, Applicants submit it is a wrong to state that fragments less than 1-130 have no SCF activity. Secondly, the specification teaches that fragments of $^{2-164}$SCF and $^{5-164}$SCF still possess some SCF-related specific activity. However, in order to expedite prosecution, applicants have amended the claim to recite "a biologically active SCF fragment comprising at least 130 contiguous amino acids of any of sequences set forth in SEQ ID NO:46, SEQ ID NO:61 or SEQ ID NO:63 that possesses an activity associated with SCF." Applicants believe this claim as amended is fully enabled by the specification as filed.

d. The Examiner's request for a teaching of all analogs of the SCF polypeptide applies the wrong standards for enablement and is therefore incorrect as a matter of law.

At pages 7-11, the Examiner expresses arguments against the enablement of the subject matter of the claims that encompasses analogs of SCF. As indicated above, the term "analogs" has been removed from claim 71 in order to expedite prosecution of that claim. However, Applicants present new claim 115, which recites:

> A composition which comprises a therapeutically effective amount of an analog of stem cell factor (SCF) polypeptide of any of sequences set forth in SEQ ID NO:46, SEQ ID NO:61 or SEQ ID NO:63 that possesses an activity associated with SCF and one or more cytokines in a pharmaceutically acceptable carrier.

At page 7, the Examiner states that "the structure and function of every analog claimed is not disclosed in such a manner such that the skilled artisan could make and use them without undue experimentation." Thereafter, the Examiner continues to posit that unless the specific structures of the analogs of SCF are given in the specification, one of skill in the art could not make or use such analogs, without undue experimentation. Applicants disagree.

The structures of numerous SCF polypeptides are taught in the specification. The

Examiner has cited two generalized texts that postulate that certain regions of a protein may be less tolerant to mutation than others. However, the Examiner has not pointed to any specific teaching in the art that one of skill in the art would be unable to produce analogs of the proteins ***of the present invention*** *i.e.*, analogs of SCF proteins.

In the cases discussed in the MPEP that held that the disclosure of an application lacked the requisite teaching to enable the scope of the claims, the Federal Circuit specifically found that the Examiner had cited art ***specific to the materials in question.*** For example, in *In re Wright*, where the claims in question covered vaccines against all RNA viruses, the Examiner had presented a 1988 reference teaching that the production of vaccines to retroviruses remained an intractable problem. In *In re Goodman*, where the claims covered protein expression in any plant cell, the examiner provided evidence that even after the filing date of the application in question, use of the claimed method in some plant cells (monocots) was not enabled (See MPEP 2164.06(b) for further discussion).

Moreover, the Federal Circuit in *In re Bundy* ruled that the disclosure of an application was sufficient to enable one skilled in the art to use the claimed analogs of naturally occurring prostaglandins even though the specification lacked any examples of specific dosages, because the specification taught that the novel prostaglandins had certain pharmacological properties and possessed activity similar to known E-type prostaglandins. (see MPEP §2164.06(b))

In the present application, the Applicants have taught numerous working examples of sequences of SCF polypeptides, based on that disclosure it would be a matter of routine experimentation to mutate the sequences to generate analogs in the scope of the claimed invention. The Court in *In re Wands* went to some lengths to define the term "experiment" as it is used in the monoclonal antibody arts. It stated that "an 'experiment' is not simply the screening of a single hybridoma, but is rather the ***entire attempt to make a monoclonal antibody.*** The process entails immunizing animals, fusing lymphocytes from the immunized animals with myeloma cells to make hybridomas, cloning the hybridomas, and screening the antibodies produced by the hybridoma for the desired characteristics." There is no credible reason for suggesting that screening a recombinant protein for a desired SCF activity would require undue

experimentation when the Federal Circuit has clearly admonished that the above screening of numerous hybridomas would not require undue experimentation.

Moreover, in *In re Wands*, the court found that Wands' carrying out the above process ***three*** times was sufficient proof of enablement to rebut the Examiner's challenge to the enablement of the disclosure. Here, as can be seen from the data presented at pages 182-185, the Applicants have repeated the entire screening process for SCF analogs no less than ***32*** separate analogs (*i.e.*, 1-178; 1-173; 1-168; 1-166; 1-163; 1-162; 1-161; 1-160; 1-159; 1-158; 1-157; 1-156; 1-148; 1-145; 1-141; 1-137; 1-130; 1-120; 1-110; 1-100; 1-133; 1-127; 1-123; 1-164; 1-183; 1-189; 1-188; 1-185; 1-180; 1-152; 2-165 and 11-164.) Applicants submit that in line with the Court's analysis from *In re Wands*, the present application has provided sufficient evidence to effectively rebut the examiner's challenge to the enablement of the disclosure.

Applicants again submit that the court has clearly articulated that as long as the specification discloses at least one method for making and using the claimed invention that bears a ***reasonable*** correlation to the entire scope of the claim, then the enablement requirement of 35 U.S.C. §112 is satisfied. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970; discussed at MPEP 2164.01(a)). The disclosure of 32 analogs of stem cell factor provide a reasonable correlation to the entire scope of new claim 115. Further, bearing in mind that the *quid pro quo* for obtaining a patent is to provide an incentive for inventors to disclose their inventions to inure to the benefit of the public, the courts have stated that an '[i]nventor should be allowed to dominate . . . others . . . based in some way on his teachings, since some improvements while unobvious from his teachings, are still within his contribution, since improvement was made possible by his work." (*In re Fisher*, 427 F.2d 833, CCPA 1970). Given that the present inventors were the first to identify a stem cell factor having the sequence of SEQ ID NO:46, 61 or 63, Applicants contend that the present inventors "should be allowed to dominate others" using analog pharmaceutical composition claims of the present invention.

e. The specification expressly teaches that the SCF polypeptides of the claimed invention may be used in the treatment of various disorders.

The Examiner disagrees with Applicants position that specification teaches that SCF has a central role in embryogenesis and hematopoiesis and demonstrates the treatment of various

stem cell deficiencies (see pages 11-12 of Office Action, paper 16). The Examiner states that the specification "does not disclose any methods or working examples of administering any SCF/cytokine composition to treat any disorder other than hematopoietic disorder" and that therefore it would require undue experimentation to determine efficacy of treatment of diseases after administration of SCF/cytokines. Again Applicants urge that this is not the appropriate standard for determining whether the claims are enabled. Working examples are not required.

The terms "central role in embryogenesis and hematopoiesis" and "capacity for treatment of various stem cell deficiencies," are not simply attorney argument, but are express teachings found in the specification of the present application (see page 18, lines 20-24). The specification goes on to state that "there are many diseases which are treatable with SCF" and then proceeds to list the disease that could be treated (page 27, lines 35-36 and 24-27). The MPEP at 2164.03 specifically states that "the examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention" and that:

> A specification disclosure . . .***must be taken as being in compliance with the enablement requirement*** of 35 U.S.C. 112, first paragraph unless there is a reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support. Assuming that sufficient reason for such doubt exists, a rejection for failure to teach how to make and/or use will be proper on that basis. In re Marzocchi, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA 1971). As stated by the court,
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> > "it is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. Otherwise, there would be no need for the applicant to go to the trouble and expense of supporting his presumptively accurate disclosure." 439 F.2d at 224, 169 USPQ at 370.

There is no reason to doubt the Applicants disclosure that the pharmaceutical compositions of the present invention possess the activity attributed to them by the Applicants. The inventors identified a novel stem cell factor and recognized that this factor may be used to treat various disorders. The fact that a specific working example of the treatment of each of the

disorders is not present in the specification does not defeat the enablement of the claimed invention directed to the effects of the pharmaceutical composition. Once the present inventors had taught individuals of skill in the art that stem cell factor could be used to treat these disorders and had taught how to make and administer compositions comprising SCF, it became a matter of routine experimentation and optimization to produce formulations for the treatment of such disorders. An inventor is not required to teach the "optimal dosage, duration and mode of administration" requested by the Examiner at page 12. These are parameters that a physician may readily determine on a case-specific basis. Such routine optimization by another does not defeat the enablement of the claims.

Subsequent to the discoveries and teachings of the present invention, those of skill in the art recognized that "SCF increases melanocyte proliferation, differentiation, survival, chemotaxis and secretion as well as accumulation *in vivo,*" and that "SCF is essential to melanocyte proliferation and differentiation." (Kawakami *et al., J. Invest. Dermatol.* 114:471-478, 2002 at page 471). Others have shown that injection of recombinant human stem cell factor compositions "promote both the hyperplasia and the functional activation of human mast cells and melanocytes *in vivo* . . . . These findings also indicate that the interaction between SCF and its receptor represents a potential therapeutic target for regulating the numbers and functional activity of both mast cells and cutaneous melanocytes." (Costa *et al., J Exp Med* 183(6):2681-6, 1996). In addition, Kawakami *et al.*, confirmed that a cytokine (TGFbeta) also is involved in melanocyte proliferation and differentiation (Kawakami et al., 2002, at page 476) and that "transforming growth factor b1 affect melanocyte precursor proliferation and differentiation in the presence of stem cell factor. . ." (see abstract on page 471). Corti *et al., Exp Neurol.*, 177(2):443-52 2002, teach results that indicate that ". . .SCF administration modulates the availability of GFP^+ cells in the brain and enhances their capacity to acquire neuronal characteristics. Cytokine stimulation of autologous stem cells might be seen as a new ***strategy for neuronal repair in neurodegenerative diseases***." (see abstract page 443).

In the face of the well-established law and the factual recognition in the specification, corroborated in the art, that SCF is a factor that can be used to treat various diseases, Applicants respectfully submit that the Examiner's position in this case is inaccurate. The specification shows one of skill in the art the various sequences of stem cell factor, the specification further

provides explicit teachings of methods of formulating pharmaceutical compositions and methods of delivering the same to a subject in need thereof. Applicants believe this guidance enables one of skill in the art to produce the SCF protein-based pharmaceutical compositions. Hence, Applicants believe the specification satisfies the enablement requirement of 35 U.S.C. §112, first paragraph. This is corroborated by the fact that studies by groups such as Kawakami et al., Costa et al. and Corti et al., confirm the efficacy of the compositions of the claimed invention.

In view of the foregoing response, Applicants submit the rejections of the claims under 35 U.S.C. §112, first paragraph for lack of enablement are overcome. Applicants request that the rejection be withdrawn and the claims be reconsidered for allowance

V. The Rejections under 35 U.S.C. §112, first paragraph for lack of written description should be withdrawn.

The Examiner maintained the rejection for the claims for lack of written description pursuant to 35 U.S.C. §112, first paragraph. In doing so, the Examiner stated that "[a]lthough the specification discloses the structure and function of numerous SCF fragments, these descriptions are not a representative number to support the description of an entire genus of functionally equivalent SCF biologically active fragments or analogs, which incorporate all SCF mutants, derivatives and fragments. . . . Furthermore, the broad brush discussion of making or screening for variants does not constitute a disclosure of a representative number of members." (Office Action, paper 16, page 14). Applicants incorporate the response of September 20, 2002 herein by reference and respectfully disagree with the Examiner's stance.

Applicants exemplified at least 32 analogs/fragments of the SCF, in addition, full SCF sequences were presented in SEQ ID NO:46, 61 and 63, thus the specification teaches at least 35 specific sequences. Applicants submit that they have met the burden of showing possession of the genus encompassed by the claims of the present invention by providing the examples discussed at pages 182-185 of the specification. As Judge Rader discussed recently in *Moba v. Diamond Automation*, the way in which the written description requirement is being applied here is as a "super-enablement rule," which is a standard that is different than for other technologies. As the Patent Statute is technology neutral, the Patent Office's stance in this case is untenable.

Once the Applicants have taught that one of skill in the art could produce the 35 sequences discussed above, it would be merely routine to produce additional sequences, because as Judge Rader indicated "to enable is to show possession, and to show possession is to enable." Therefore, Applicants submit that the specification provides a detailed description of representative SCF sequences encompassed by the claims, the specification teaches those of skill how to make variants of those sequences, and therefore, Applicants have shown possession of the claimed invention. Applicants believe that the recent decisions of the Federal Circuit also support this contention. (See discussions in *Moba v. Diamond Automation* and in *Enzo Biochem, Inc. v. Gen-probe, Inc.*, 63 USPQ 2d 1609, 1628 (Fed. Cir. 2002)). In light of the case-law and the explicit teachings of the present invention, Applicants submit that the rejection of the claims based on 35 U.S.C. §112, first paragraph, for lack of written description should be withdrawn.

VI. Concluding Remarks.

In view of the above amendments and remarks, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Applicants respectfully request a withdrawal of the rejections and an indication of allowance of the application. Should the Examiner have any questions regarding this submission, she is cordially invited to contact the undersigned representative.

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Respectfully submitted,

By_____

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